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PATENT
Attorney Docket No. **OPHD-06331**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: John A. Kink
Serial No.: 09/832,233 Group No.: 1617
Filed: 04/10/01 Examiner: Sharareh, S.
Entitled: **Prevention and Treatment of Necrotizing Enterocolitis**

APPELLANTS BRIEF TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: November 23, 2004 By: Traci L. Light

Sir or Madam:

Enclosed herewith, please find the Appellants Brief in triplicate, as well as a check in the amount of **$340.00** to cover the cost of filing said brief.

The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. **08-1290**. **An originally executed duplicate of this transmittal is enclosed for this purpose.**

Dated: November 23, 2004

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APPELLANTS BRIEF

APPEAL NO.:

ATTENTION: Board of Patent Appeals and Interferences
Commissioner for Patents and Trademarks
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner of Patents, Washington, D.C. 20231, on November 23, 2004.

By Traci E. Light

Sir/Madam:

This Brief is in furtherance of the Notice of Appeal mailed on September 30, 2004.

The fees required under § 1.17(c) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Brief is transmitted in triplicate. [37 CFR § 1.192(a).]

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This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]:

I. REAL PARTY IN INTEREST

The real party in interest is Promega Corporation, 2800 Woods Hollow Road, Madison WI 53711-5399.

II. RELATED APPEALS AND INTERFERENCES

There are no related applications pending appeal.

III. STATUS OF CLAIMS

The present application (09/832,233), as filed on 04/10/01, contained Claims 1-14 as a continuation of copending application (09/318,109; filed on 05/24/99, and issued as US Pat. No. 6,214,343 on 04/10/01). A First Non-Final Office Action (mailed 09/24/02) resulted in a response amending Claims 1 and 9 (mailed 03/20/03). A First Final Office Action (mailed 06/10/03) resulted in a response (filed as a First RCE) again amending Claims 1 and 9 (mailed 10/08/03). A Second Non-Final Office Action (mailed 12/31/03) resulted in a response amending Claims 1 and 9 for a third time and canceling Claim 6 (mailed 03/31/03). A Second Final Office Action (mailed 07/01/04) rejected Claims 1-5 and 7-14, resulting in filing a Notice Of Appeal (mailed 09/30/04).

These claims, as they now stand, are set forth in Appendix A (attached at Tab 1).

IV. STATUS OF AMENDMENTS

All amendments in the case have been entered.

V. SUMMARY OF THE INVENTION

The present invention relates to therapeutics for the prevention and treatment of necrotizing enterocolitis, and in particular the prevention and treatment of necrotizing enterocolitis (NEC) in neonates through the use of antibody therapy. In particular, one example of the present invention demonstrates a novel finding that antibodies against tissue necrosis factor (TNF) are effective in preventing NEC.

It is preferred that the antibodies not be complement fixing. More specifically, avian antibodies (*e.g.*, chicken antibodies from eggs) are preferred. (See Claims 1 and 9). It is contemplated that the treatment with such antibodies will have the desired result of reducing mortality rates caused by NEC.

In one embodiment, the present invention contemplates a method comprising the administration of antibodies which binds to an inflammatory mediator such as TNF. Preferably, the antibody is reactive with TNF across species. Thus, the present invention provides anti-TNF antibody that will react with mammalian TNF generally.

The present invention also contemplates a method for reducing the symptoms of NEC. In one embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a neonate with symptoms of necrotizing enterocolitis; ii) a therapeutic preparation comprising polyclonal avian anti-TNF antibodies and (b) administering said antibodies to said neonate (See Claim 1) under conditions wherein at least one of said symptoms is reduced. (See Claim 11).

In another embodiment, the present invention contemplates a method of treating neonates at risk for NEC. In another embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a neonate at risk for necrotizing

enterocolitis; ii) a therapeutic preparation, comprising polyclonal avian anti-TNF antibodies and (b) administering said antibodies to said neonate (*e.g.*, administering to the intestinal lumen of said neonate). (See Claim 9).

In various other embodiments, the route of administration may be selected from intravenous, oral, parenteral, and rectal. (See Claims 2, 3, 4, 5, 12, 13 and 14).

VI. ISSUES

There is one issue on appeal:

A. The Examiner Has Failed To Make A *Prima Facie* Case Of Obviousness

The Examiner fails to make a *prima facie* case of obviousness because the asserted reference combination does not: i) disclose all of the claim limitations; ii) offer any motivation for the combination; and iii) teach any reasonable expectation of success.

In the last Office Action Response, the Applicants successfully overcame an obviousness rejection based upon Ebil II as the primary reference, in view of Muguruma *et al.*, Eibl I, and Wolf *et al.* The Applicants submit that the Examiner has added the Le *et al.* reference which has the same admitted deficiencies as Ebil II. The Examiner, therefore, has unnecessarily continued the pending examination by re-presenting the same unsupported argument using a different set of references.

Further, in the present rejection (*i.e.*, *Second Final Office Action*), the Examiner increases the number of cited references from four (4) to six (6) by adding Le *et al.* (US Pat. No. 5,656,272) as an alternative primary reference and, Williams *et al.* (US Pat. No. 5,601,823) as an additional secondary reference.[1]

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[1] The Board is reminded that the Federal Circuit views an ever increasing number of cited references to support a 103(a) rejection as an indicator of non-obviousness.

VII. GROUPING OF CLAIMS

Each claim stands alone. Each claim has distinct limitations and must be considered independently.

Independent Claim 1 specifies a method of treatment comprising a human neonate having symptoms of necrotizing enterocolitis and a purified avian anti-TNF polyclonal antibody, wherein the antibody is administered to the human neonate. For example, this claim is not limited by the nature of the neonate or the route of administration. Dependent Claims 2, 3, 4, and 5, respectively, further specify that the antibody may be administered intravenously, orally, parenterally, or rectally. Dependent Claims 7 and 8, respectively, further specifies that the avian antibody is from a chicken, and wherein the antibody is produced in a chicken egg. Dependent Claim 11, further specifies that antibody administration reduces necrotizing enterocolitis symptoms.[2]

Independent Claim 9 specifies a method of treatment comprising a neonate at risk for necrotizing enterocolitis and a purified avian anti-TNF polyclonal antibody, wherein the antibody is administered to the lumen of the neonate. For example, this claim is not limited by the species, sex, or age of the neonate. Dependent Claim 10, further specifies that the neonate is a low birth weight neonate. Dependent Claims 12, 13, and 14, respectively, further specify that the antibody may be administered intravenously, orally, parenterally or rectally.

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[2] The Board should take note that, upon remand to the Examiner, the Applicants will formally amend Claim 11 to properly depend from Claim 1.

VIII. ARGUMENT

A. Claims 1-5 & 7-14 Are Not *Prima Facie* Obvious

The Examiner has not properly established the *prima facie* obviousness of the rejected claims. For example, the Examiner makes the conclusory statement:

> The role of TNF as a pro-inflammatory mediator in development of NEC has been well established in the art as shown by Muguruma, Wolf and Eibl I. Therefore, even though Le does not explicitly disclose the use of anti-TNF antibodies in treating NEC in neonates, it would have been obvious to one of ordinary skill in the art at the time of invention to employ such products for treatment of NEC, because as suggested by Eibl II, Muguruma and Eibl I and Wolf, TNF plays an integral role in development of NEC and the ordinary skill in the art would have had a reasonable expectation of success in employing the anti-TNF of Le for treating NEC. Furthermore, one of ordinary skill in the art would have been motivated to formulate an avian polyclonal anti-TNF, because as suggested by Williams such type of antibodies can be administered orally, are non-immunogenic and are well tolerated by infants. *Second Final Office Action* 07/01/04 pg. 3.

The Applicants disagree because the Examiner's statements are: i) unsupported, improper, and contain bald conclusions without a factual basis; and ii) do not meet the proper standards to establish a *prima facie* case of obviousness.

B. The *Prima Facie* Standards Of Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above

requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicants submit that the Examiner's rejection does not meet these criterion.

As a preliminary matter, when dealing with a rejection based upon obviousness it is essential for the Examiner to view the claimed embodiment as a whole:

> [T]he question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious. Consideration of differences, like each of the findings set forth in *Graham*, is but an aid in reaching the ultimate determination of whether the claimed invention *as a whole* would have been obvious.

Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1537, 218 USPQ 871 (Fed. Cir. 1983) (emphasis in the original). It is clear to the Applicants that the Examiner has not "stepped back" from the elements to actually "see" the claimed embodiment. Specifically, the Examiner creates the obviousness rejections by "picking and choosing" specific elements among the cited publications and subsequently uses the specification in hindsight.[3] The Federal Circuit has noted that: "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch,* 972 F.2d 1260, 1266 (Fed. Cir. 1992). The Applicants note that the Examiner's conclusions allegedly establishing a *prima facie* case of obviousness are not supported by cited reference quotations.

C. The References Do Not Teach "An Anti-TNF Antibody" For Treating Necrotizing Enterocolitis

The Examiner admits that Le *et al.* (US Pat. No. 5,656,272) does not teach an anti-TNF antibody: "Le fails to specifically teach anti-TNF use for treating Neonatal Necrotizing Enterocolitis (NEC)." *Second Final Office Action,* pg. 2. The Applicants submit that Le *et*

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[3] A practice not permitted under patent law. *See, In re Rouffet, 149 F.3d 1350, 47 USPQ.2d 1453 (Fed. Cir. 1998); and In re Warner,* 379 F.2d 1011, 154 USPQ 173 (CCPA 1967).

al. also fails to properly disclose NEC. Even if Le *et al.* did mention necrotizing enterocolitis (which is does not) this would only be an "invitation to try", a rejection basis also forbidden by the Federal Circuit.[4]

The Examiner admits that Ebil II (US Pat. No. 5,833,984) does not teach an anti-TNF antibody: "Eibl fails to specifically use anti-TNF antibodies in treating NEC." *Second Final Office Action*, pg. 2. Instead of advocating that necrotizing enterocolitis should be treated by specific anti-TNF antibodies, Ebil II teaches TNF-α release inhibition by IgA multimer complexes that also sequester circulating TNF-α:

> ... human serum IgA, which is largely monomeric, inhibits monocyte cytokine release. Heat aggregation, which forms IgA multimers, enhances the inhibitory effect of IgA on TNF-α release.

Ebil II, col 7 ln 66 - col 8 ln 2. Ebil II, therefore, teaches that necrotizing enterocolitis immunotherapy does not involve direct neutralization by specific antibodies (*i.e.*, for example, anti-TNF antibody).

The Examiner admits that Wolf *et al.* (Acta Pediatr Suppl 396:37-40 (1994)) does not teach anti-TNF antibody: "Wolf, for example, describes the general knowledge about the effects of oral IgA-IgG preparations ..." *Second Final Office Action*, pg. 3. Even if Wolf *et al.* disclosed anti-TNF antibody (which is does not), Wolf *et al.* provides support for the hypothesis that immunotherapy inhibits the release of TNF-α:

> The purpose of the present study was to investigate whether the oral IgA-IgG preparation used for prophylaxis of NEC might have regulatory effect on the release of inflammatory cytokines like TNF alpha and IL-6 by human monocytes.

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[4] "An invention is 'obvious to try' 'where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.'" *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988).

Wolf et al., pg.38 rhc. Wolf *et al.,* therefore, teaches that necrotizing enterocolitis immunotherapy does not involve direct neutralization by specific antibodies (*i.e.*, for example, anti-TNF antibody).

The Examiner admits that Ebil I (NEJM 319:1-7 (1988)) does not teach anti-TNF antibody: "Eibl I sets forth successful use of IgA-IgG ..." *Second Final Office Action*, pg. 3. Not only is Eibl I silent on anti-TNF antibody, Eibl I is also silent on TNF-α.

The Examiner admits that Muguruma *et al.* (Prenat Neonate Med 3:571-579 (1998)) does not teach anti-TNF antibody: "Muguruma et al., however, fails to specifically teach the use of antibodies ..." *Second Final Office Action,* pg. 3. Even if Muguruma *et al.* disclosed anti-TNF antibody (which is does not), Muguruma *et al.* provides evidence that TNF-α may not directly cause necrotizing enterocolitis:

> Although we were successful in producing a full thickness hemorrhage by the treatment with these agents [TNF-α & LPS], a clearly identifiable necrosis was not evident (Tables 2 and 3).

Muguruma et al., pg. 578 lhc. The Board must recognize that Muguruma *et al.* does not disclose anti-TNF antibodies and casts doubt on whether or not TNF-α is directly responsible for necrotizing enterocolitis.

The Examiner admits that Williams *et al.* (US Pat. No. 5,601,823) does not teach anti-TNF antibody: "Williams is merely used to show the state of the art in formulating polyclonal avian antibodies for treating inflammatory enterocolitis caused by *Clostridium difficile.*" *Second Final Office Action,* pg. 3. Not only is Williams *et al.* silent on anti-TNF antibody, Williams *et al.* is also silent on TNF-α.

It is easily seen that the Examiner has not offered a single reference that discloses an anti-TNF antibody used for treating necrotizing enterocolitis. Consequently, on this fact alone, the obviousness rejection fails.

D. The References Provide No Motivation To Combine

As detailed above, the Examiner's belief that the cited references teach the use of anti-TNF antibodies for treatment of NEC is simply wrong. The Examiner has pointed to no statement in any reference that suggests an antibody to a TNF antigen would be useful to treat NEC. The Applicants point out that Ebil II provides teachings regarding IgA that are contrary to the teachings in both Wolf *et al.* and Ebil I[5], for example:

> ... IgG appears to actually enhance inflammatory activity, which is undesirable. Accordingly, it is preferred to use IgA which is essentially free of IgG.

Ebil II, col6 ln 31-34. Ebil II also teaches away from the Applicants' claimed embodiment by disclosing that a non-specific antigen/antibody interaction is the preferred approach to immunoprotection against necrotizing enterocolitis:

> This effect [when using IgA/IgG] is believed to be a result of the formation of antigen-antibody **complexes** caused by high titers of antibodies against a multitude of potential pathogens and their toxins.

Ebil II, col 2 ln 24-27 [emphasis added]. Clearly, the Examiner's assumption that an unstimulated crude fractionated IgA-IgG plasma preparation is equivalent to anti-TNF antibody (as described in the Applicants' specification) demonstrates a basic misunderstanding of Applicants' claimed embodiment and is contrary to level of skill in the art.

The Applicants conclude, therefore, that the Examiner cannot point to any statement in the combination of Le *et al.*, Eibl II, Muguruma *et al.*, Eibl I, Wolf *et al.*, or Williams *et al.*

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[5] Both Wolf *et al.* and Ebil I teach IgA/IgG combinations.

that suggests or motivates one skilled in the art to generate an anti-TNF antibody to treat NEC. The Examiner has failed to indicate where in the references cited there is such a suggestion of desirability to combine. The Examiner must provide a basis for combining art prior to considering the combination. Indeed, the requirement that the Examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). There are three sources for this evidentiary component: the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999).

Instead, the Examiner presupposes to be "one skilled in the art". The Examiner is reminded that - under the law - an Examiner is NOT one skilled in the art; mere opinion of the Examiner on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art.").

The Examiner has the burden of showing that the cited art is justified by "evidence" which supplies a suggestion, teaching or motivation sufficient to provide one skilled in the art to create the Applicant's invention.

Looking at the cited references themselves, there are no objective teachings that would lead that individual to create the Applicant's invention. Indeed, the Examiner points to nothing in the references themselves which teach or suggest the invention. In this manner, the Examiner has not satisfied his burden under the law. *See In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears.").

Because there are no suggestions or motivations within the cited references to support the Examiner's combination, the rejection fails.

E. The References Do Not Teach Reasonable Success

The Examiner attempts to establish this prong of *prima facie* obviousness by stating:

> ... it is well established that TNF potentiates the progress of NEC and thus reducing the effects of TNF activity among human infants would improve or alleviate the pathological changes that would lead to NEC. *Examiner states that any degree of relief for NEC would read on the scope of the instant claims*, and the ordinary skill in the art would have had a **reasonable expectation of success** in at least observing some symptomatic relief when administering the anti-TNF **taught by Eibl**.

Second Final Office Action, pg. 4 [emphasis added]. At the outset, the Applicants reiterate that the Examiner's statement that Eibl II teaches NEC treatment by anti-TNF is erroneous (*supra*). Further, the Federal Circuit requires any reference asserted for an "expectation of success" to explicitly predict that the recited claims will work. *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Consequently, it is the Examiner who is making the conclusions that "reducing the effects of TNF activity among human infants would improve or alleviate ... NEC", **not** "one having ordinary skill in the art". As asserted above, the Examiner is continuing to speculate without a factual basis.

One example regarding the Examiner's lack of facts is that three (3) of the asserted references (Ebil II, Wolf *et al.*, and Ebil I)[6] all teach preparations of IgA and/or IgG that are merely fractionated plasma extractions:

> Preferably, a plasma fraction is used as a source of IgA. For example, an IgA fraction can be obtained by ion exchange chromatography, hydrophobic chromatography, hydrophilic chromatography or affinity chromatography of a plasma fraction ...

Ebil II, col 8 ln 10-14. The Board is reminded that the production of specific anti-TNF antibodies require immunization procedures. TNF immunization is not taught by these references and, therefore, these references cannot explicitly predict the success of using anti-TNF antibodies.

Additionally, the Examiner has misconstrued the pending claims by stating that: "... any degree of relief for NEC would read on the scope of the instant claims ..." (*supra*). The Examiner has erroneously concluded that these claims encompass reduced TNF activity by any means.

This rejection must fail because when the cited references fail to disclose a specific claim element (*supra*) the references clearly cannot explicitly predict the claim's success.

IX. CONCLUSION

Appellants submit that, with due consideration to all these factors discussed above, the patentability of Claims 1-5 and 7-14 is evident. The standards regarding a *prima facie* case of obviousness are not met against the Examiner's cited references. Consequently, the rejection fails.

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[6] These three cited references share common inventors and disclose the same technology.

For the foregoing reasons, it is submitted that the examiner's rejection of Claims 1-5 and 7-14 was erroneous, and reversal of this rejection is respectfully requested.

Respectfully submitted,
MEDLEN & CARROLL, LLP

Dated: Nov 23, 2004

By: _____
Peter G. Carroll
Reg. No.: 32,837

Attorneys for Appellant

APPENDIX A: CLAIMS INVOLVED IN THE APPEAL

1. A method of treatment for necrotizing enterocolitis, comprising:

   a) providing:

      i) a human neonate, wherein said human neonate has symptoms of necrotizing enterocolitis;

      ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibodies, and;

   b) administering said formulation to said human neonate.

2. The method of Claim 1, wherein said administering is performed intravenously.

3. The method of Claim 1, wherein said administering is performed orally.

4. The method of Claim 1, wherein said administering is performed parenterally.

5. The method of Claim 1, wherein said administering is performed rectally.

7. The method of Claim 1, wherein said polyclonal avian antibody comprises chicken antibody.

8. The method of Claim 7, wherein said chicken antibody is derived from chicken eggs.

9. A method of treatment for necrotizing enterocolitis, comprising:

   a) providing:

      i) a neonate at risk for necrotizing enterocolitis,

      ii) a therapeutic formulation comprising purified avian anti-TNF polyclonal antibody, and;

   b) administering said formulation to the lumen of the intestine of said neonate.

10. The method of Claim 9, wherein said neonate is a low birth weight neonate.

11. The method of Claim 9, wherein said administering reduces said symptoms.

12. The method of Claim 9, wherein said administering is performed orally.

13. The method of Claim 9, wherein said administering is performed parenterally.

14. The method of Claim 9, wherein said administering is performed rectally.